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Science

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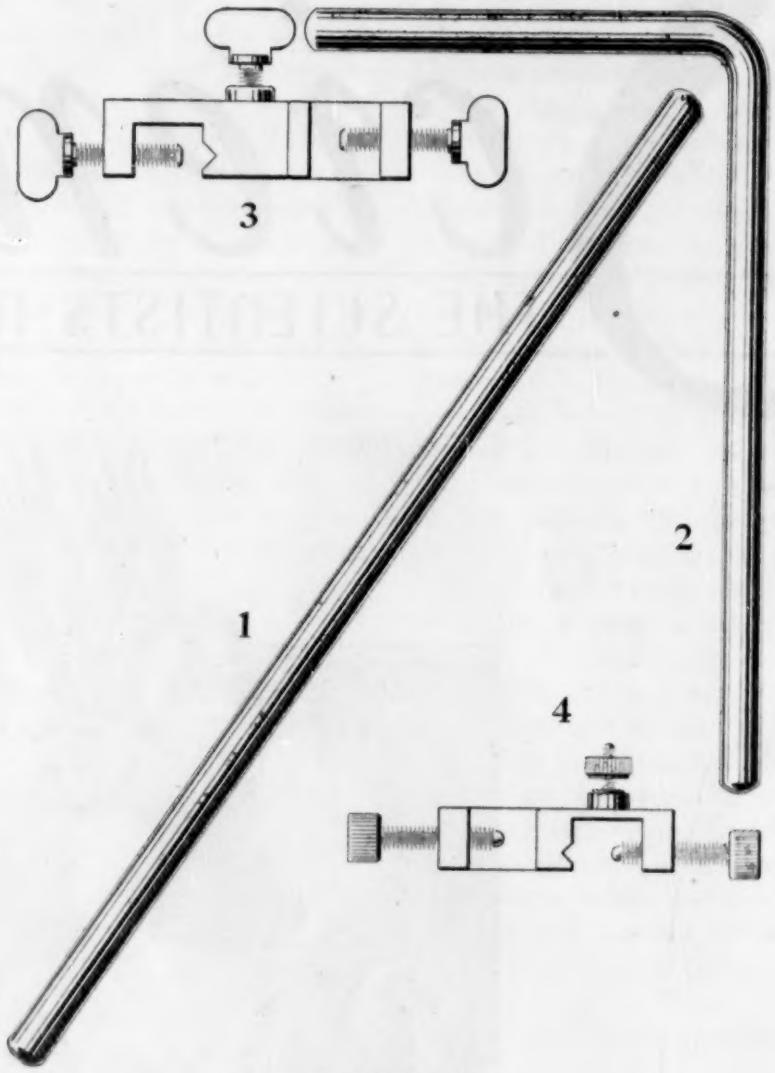
The Native Protein

Dorothy Wrinch

For PHYSIOLOGICAL *and other* LABORATORIES



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The Native Protein

Dorothy Wrinch

Department of Physics, Smith College, Northampton, Massachusetts

RESULTS OBTAINED IN PHYSICAL chemistry and chemical crystallography yield a rather definite picture of the native protein which fits at many points with that emerging from the various fields of the biology of the proteins, *i.e.* enzymology, immunology, pharmacology, virus studies, and genetics. If we attempt to sum up the general impression derived from a study of various independent sources of information on the proteins, it can be broken down into the following parts:

(1) Many proteins in solution are particles, not individual molecules (*21*). It is useful to use the term *proteon* to connote a native protein unit incapable of division into subunits also having the native protein character. Every native protein may then be regarded as a proteon or a system of proteons, alike or different. That a protein particle is not a mere conglomerate of proteons but an orderly aggregate, *i.e.* a molecular colony, follows from the finding that in many cases where ultracentrifugal studies show that a protein is uniform in size and shape under well-defined external conditions, the protein in question is capable of dissociation into subunits when the environmental conditions are modified (*21*). Much information has now been assembled concerning the particle status of many proteins, ranging from the very large tobacco mosaic nucleoprotein down to horse hemoglobin. The reversible dissociation of protein particles does not imply any change in the chemical status of the proteons. It is therefore to be sharply distinguished from denaturation.

(2) Interproteon associations within particles depend upon the R-substituents of the amino acid backbones ($N—C_\alpha—C$) which make up the proteon skeletons. Structure chemistry provides three types of association: direct polar, mediated polar, and less polar. Horse hemoglobin, which on dilution dissociates into two subunits, provides an illustration of the first type; the Helix hemocyanin particle whose dissociations in aqueous solution are affected by Ca^{++} and Mg^{++}, an illustration of the first and second types (*21*). That the less polar R-substituents of aliphatic and aromatic types, as well as the more polar types, emerge from protein surfaces is indicated by many data, e.g. the higher solubility of insulin in propylene glycol than in water and the affinity of human serum albumin for the paraffin chains of fatty acid molecules (*13*). Thus, associations of the third type are also a possibility, and the fact that studies in aqueous solution give two subunits per particle (e.g. for horse hemoglobin) does not preclude the possibility that these subunits may themselves be particles in which the proteons are associated by less polar R-groups. Such a situation is increasingly indicated by crystallographic studies (*6*).

(3) The proteon skeleton is an *intrinsically unstable structure*. This is seen, for example, in the fact that each protein has its own pH stability range. Its stability depends upon the energy provided by the association of favorably placed polar R-substituents which can be direct or mediated by foreign molecules or ions. The minimum solubility of a protein in the neighborhood of its isoelectric point and the general instability of proteins on dilution (*4*) are further indications of this situation. The fact that the proteon, apart from its R-groups, is unstable means that there is, in the skeletons of native proteins, a labile bond. That the protein skeleton is rigid, we know from both crystallography (*6*) and physical chemistry (*10*). Evidently it is this labile bond which is responsible for the rigidity. That the labile bond joins skeletal atoms and not atoms belonging to R-substituents is inherent in the viewpoint which emerges from chemistry as a whole. Just as the sterol skeleton embodies the sterol character, the protein skeleton embodies the protein character, irrespective of the particular amino acid compositions of individual proteins. To reject this viewpoint is to exclude the proteins from the fabric of present-day chemical ideas. The protein molecule may be viewed as a triumph of atomic engineering in which there is a "compression" member comprising the skeletal atoms and a "tension" member comprising the R-substituents with hydrogen bridges and hydrogen bridge circuits as "ties." The relation between the skeleton and the associational complex of its substituents is thus essentially symbiotic. Only with the stabilization energy provided by the associations of its substituents can the skeleton continue to exist; only so long as the skeleton remains intact are the sites or roots of the substituents held in spatial positions which permit the formation of associations. In the associational complex of substituents resides the physicochemical individuality of a proteon; upon it depends its biological specificity.

The Protein Skeleton

The major unsolved problem in the structure of proteins is the nature of the protein skeletons. It is to be expected that these skeletons are entities as definite as, for example, the carbon skeleton of the sterols or the carbon-

Based upon the Stieglitz Memorial Lecture, American Chemical Society, Chicago, January 1947.

nitrogen skeleton of hexamethylene tetramine. The information required, before fundamental progress in understanding protein structure can be made, is a blueprint showing the positions in space of every N, every C_α and every C in the skeleton or skeletons. It is necessary, therefore, to discover how the (N—C_α—C) units are interlocked to form a rigid skeleton and, incidentally, the number or numbers of amino acid residues capable of building such integrated structures.

One important issue, generally the first to be discussed in an analytic study of an unknown structure, is symmetry. The fact that all the (N—C_α—C) units in proteins have the C_β atom attached to the C_α in the same (levo-) position narrows the possibilities regarding the symmetries of protein skeletons, since it eliminates all types involving a center of symmetry or a mirror plane. Twelve possibilities comprise: two cubic, O and T; two hexagonal, D_6 and C_6; two rhombohedral, D_3 and C_3; three tetragonal, D_4, C_4, and S_4; one orthorhombic, D_2; one monoclinic, C_2; and one triclinic, C_1. Each will require investigation in turn. So far only cubic symmetry has been considered (*25*). So many facts regarding proteins fall into place if it is assumed that protein skeletons have cubic symmetry that this assumption and its far-reaching implications merit detailed investigation and study. The hypothesis at once explains how it can happen that a number of proteins, unlike organic molecules in general, form crystals of high symmetry (*6*, *7*). It explains, also, the variety of space groups exhibited by protein crystals (*6*, *7*). The body of knowledge comprised in the atomic structure of minerals (*2*) shows exactly the lines upon which such a situation can arise, provided a cubic skeleton is characteristic of all proteons. Proteons form particles, often of immense molecular weights, which, to the limit of sensitivity of the ultracentrifugal technique, are uniform in shape (*21*). The cubic hypothesis explains how this can happen. Molecules built on cubic skeletons can form particles by the association (as it were) of faces, edges, or vertices, after the manner of the silicates (*2*), thereby building aggregates which are of definite morphology, even though they may be large. There seem to be many indications that only a cubic skeleton can build particles of definite morphology having the variety of shapes exhibited by protein particles. The variety of optical characters (*12*) is also explained. Since the cubic skeleton is necessarily isotropic, the optical character of a protein crystal depends upon the nature and arrangement of its particular R-substituents.

In this connection, the idea presents itself that a local situation on the surface of a protein molecule or within a protein particle may be, to all intents and purposes, a replica of a local situation in a mineral (*26*). Metals ions are known to be associated with many proteins, e.g. manganese with arginase, zinc with carbonic anhydrase, copper with phenolases, iron with catalase, peroxidase, cytochromes, and lactic dehydrogenase. With mineral precedents in mind, we can picture a metallic ion, for which a tetrahedral or an octahedral environment of oxygens is appropriate, clamping together protein molecules, each carrying glutamyl or aspartyl substituents. We can also picture hydrogen bridge circuits, of the types found in ice (*1*) and in various organic crystals, such as pentaerythritol (*5*) and acetamide, (*18*) engaging substituents of protein molecules. Such situations involve symmetry elements also. A cubic skeleton permits, though it does not require, such associational complexes of its substituents. It would also permit the integration of individual hydrogen bridge circuits by water molecules into a multiply-connected network covering the whole molecule. Proton jumps or transfers, of the type already postulated in ice, would then allow the entry and exit of protons at widely separated points. The suggestion may be made that the essence of a protein capable of enzymatic activity may reside in such a network over its surface. Long-range forces for proteins, which have been postulated for some time, provide, it would seem, the only explanation of biological phenomena such as those concerned with the pairing of chromosomes and the mitotic cycle in general (*22*). They have recently been postulated, even more definitively, on the basis of revolutionary results concerning protein interactions at distances of the order of 100 A. (*14*, *15*). That an enveloping network of multiply-connected hydrogen bridge circuits may prove to be the seat of such forces is worthy of the most careful consideration.

A Theory of Biosynthesis

Whether our concern is with the possibility of long-range forces or with the nature of enzymes, protein function may be regarded as the outward sign of an inner essence. It is therefore to be expected that the most fundamental of all protein functions, the production of replicas, may throw light upon the nature of protein structure. (It is of interest in this connection that the function of replication is gradually being extended to more and more proteins, *20*.) A theory of biosynthesis is therefore presented for consideration. It is based upon the belief that replication is akin to crystal growth and so belongs essentially to the domain of crystallography, the richest repository of ideas for structure studies in general and indispensable in any attempt to understand the proteins.

The replication of proteins falls into two parts: the replication of protein molecules and the assembling of protein molecules into protein particles. The former is the crucial happening in protein synthesis.

For molecular replication, three basic assumptions are required:

(1) We assume that the inherent capacity of certain species of protein to produce replicas depends on the presence on their surfaces of *active patches* (to use Warburg's term), *i.e.* local specific constellations of R-sub-

stituents. Each of these, we must presume, can function as a mold or templet, permitting the laying down on itself of a complementary constellation. Under what circumstances, then, will such constellations provide appropriate material for new, hitherto-non-existing proteons which are exact replicas of those already existing? Evidently, in the first place, this occurs only if a proteon is in some sense, a surface structure—a stiff fabric of some kind forming a 'space-enclosing' shell. This requirement accords well with the fact that all proteins, no matter how large they may be, produce monolayers of the same thickness, 7–11 A. Secondly, it is necessary that the constellations complementary to those comprising an existing proteon be equivalent to the constellations themselves. Thus, we might take a molecule of the same shape as, for instance, hexamethylene tetramine, but larger and analyze its surface into various patches. Suppose now that each patch of the surface is complementary to the antipodal patch. This would mean that the patch synthesized on, and complementary to, one part would actually be the antipodal patch. In such a case, then, the synthesis by individual molecules of complementary patches would *ipso facto* produce the patches capable, when correctly assembled, of making new molecules which are exact replicas. Thus, the first deduction to be made regarding protein molecules is that they are surface structures, comprising a set of individual patches which form a self-complementary set.

(2) In order to have a mechanism whereby these isolated constellations on different molecules may, on occasion, be integrated so as to interlock, in the same spatial pattern as in the original molecules, something has to be postulated regarding the capacity of the original molecules to form orderly assemblies. In such a case, we can picture the incipient crystallization of the existing molecules permitting complementary patches to interlock, step by step, in a variety of sequences, into precisely the pattern in which the patches are integrated in the existing molecules. We see then that the global self-complementariness of the surface of a protein molecule belonging to a species capable of replication can be more precisely defined. It must be "crystallographically satisfactory"; the incipient crystallization of existing molecules then so sets the individual complementary patches that interlocking into new and identical molecules results. In the example cited, the antipodal patches form pairs of complementary patches. In the case of the phosphotungstic acid anion, patches of the surface are self-complementary. There are, in fact, a well-defined number of ways in which a crystallographically satisfactory global self-complementariness can be achieved. One of these ways must be characteristic of the synthesizing proteins; which, we do not yet know. It is worth emphasizing that whichever alternative is adopted by proteins, one apparent difficulty disappears. It has been stated that there is some objection to postulating the formation of a complementary pattern, since a protein produces not a complementary pattern but a replica of the original (*3*). The difficulty evanesces when it is seen that the molecule results from the integration of individual complementary patches, which may be, but need not be, replicas of the patches on which they are synthesized, and that it is only the appropriate *global self-complementariness* of the molecules which ensures replication.

(3) The energy questions involved in protein synthesis point in the direction of certain ancillary molecules being present during such operations, e.g. molecules containing energy-rich phosphate bonds. It should be noted in this connection that among the many crystalline *nucleo* proteins already well known, bushy stunt virus nucleoprotein achieves even a *cubic* space group (*7*). That nucleic acid plays an essential role in replication has long been assumed (*20, 24*).

Protein Intermediates

This theory of biosynthesis has a number of implications, some of them far reaching. It is sufficient here to refer to one of them—the existence of protein intermediates. These may be visualized as the various individual active patches upon which complementary constellations are formed. There are indications that such structures may already have been found in no less than a dozen cases, e.g. in the lactalbumin precursor (*19*), in the digestion products of beef pseudoglobulin (*11*), β-lactoglobulin (*8*), and casein (*23*), and in hydrolytic products of silk (*9*). These products are all of low molecular weight corresponding to amino acid residue numbers in the range 4–12, clearly indicating that the smallest—perhaps the only—proteon skeleton may comprise relatively few residues. It is to be emphasized that the products in the last case have biological activity, connoting a definite structure. Biological activity has been found in protein monolayers in a variety of cases which include ovalbumin, horse serum albumin and globulin (*17*), and insulin and metakentrin (*16*). In the case of the globulin, it proved necessary to compress the film to 15 dynes or so (*17*). A structure capable of biological activity only under such circumstances may well contain a labile bond. All these facts point to one conclusion, which is exactly that reached in the discussion of biosynthesis. The proteon, it would seem, is an integration of parts of definite structure and individuality. The immense difficulty of the study of the *structure* of proteins (in contrast to *composition* of proteins) by way of organic chemistry needs no emphasis. But a new approach opens when we think in terms of protein intermediates and aim at a more limited objective. The application of the general ideas which presented themselves in the consideration of the symmetry of the protein skeletons to the possible structure of such protein intermediates yields various specific suggestions regarding the particular amino acid residues which may be expected in conjunction (*26*). A systematic study of the

amino acid compositions to be expected of active patches can now be undertaken. The complete characterization of protein intermediates and their resynthesis would mark a crucial stage in protein studies.

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Tidal Illumination Diagrams

H. R. Seiwell

Woods Hole Oceanographic Institution[1]

THE TIDAL ILLUMINATION DIAGRAM IS one of the various graphic devices designed during the recent war to represent significant hydrographic conditions on military targets. It was introduced by the Oceanographic Section of Headquarters, Army Air Forces, in 1942 to represent relationships between stage of the tide and state of illumination in target areas of Northwest Africa. Later, its use was extended to all theaters, and preparation on a mass scale was taken over by the U. S. Coast and Geodetic Survey, where facilities are available for computation and graphic presentation of these data for many parts of the world. Recent comments have shown the diagrams to be of practical use in this postwar period.

The tidal illumination diagram is so arranged that for any hour of the day combinations of solar illumination and stage of the tide are readily noted. Heights of high and low tides are referred to the sound datum of nautical charts of the specific locations. In so far as possible, tidal data from the U. S. Coast and Geodetic Survey tide tables are used. The occurrences of high and low tides are shown as a series of connected points enabling the user to visualize the changing sequence throughout the month. Days of the month are represented by vertical lines covering the period from noon through midnight to noon of the next day.

Three types of twilight are indicated to bring out gradation in light from sundown to darkness and from darkness to sunrise. Civil twilight begins with sunset and ends when the sun is 6° below the horizon. During this period, objects may be distinguished readily, and a newspaper may be read without the aid of artificial light. At its end,

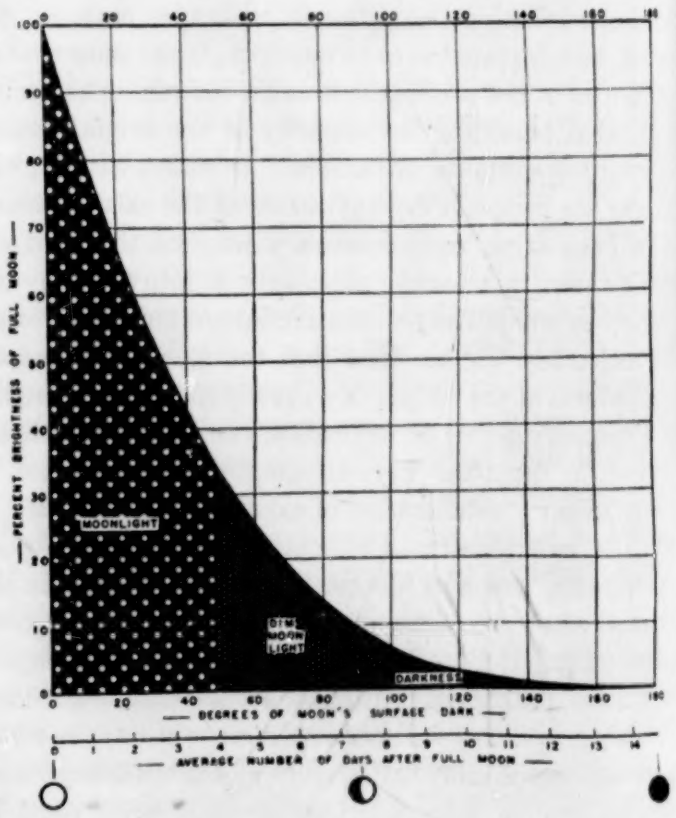

FIG. 1. Relative brightness of moon with change of phase.

sky brightness is approximately 20 times that of the full moon at zenith (Fig. 1). In the following period of nautical twilight, the brighter stars are visible, the horizon is

[1] Contribution No. 382.

nerally indistinguishable, but general outlines of objects not too distant can be distinguished. Astronomical twilight begins when the sun is 12° below and ends when it is 18° below the horizon. During this period, illumination is distinctly brighter than during complete solar darkness but less than during periods of dim and brilliant moonlight (Figs. 2 and 3).

Variations in moonlight intensity are arbitrarily divided into periods of bright and dim moonlight. Bright moonlight is taken as the period from four days before to four days after the appearance of full moon, during which time light intensity varies between full moon brightness at its zenith and about one-third of this value (Fig. 1). The period of dim moonlight includes four days prior to the beginning of bright moonlight and four days after its end, during which time illumination intensity varies from about one-tenth of full moon brightness at zenith. The relative brightness of the moon with phase is illustrated by Fig. 1.

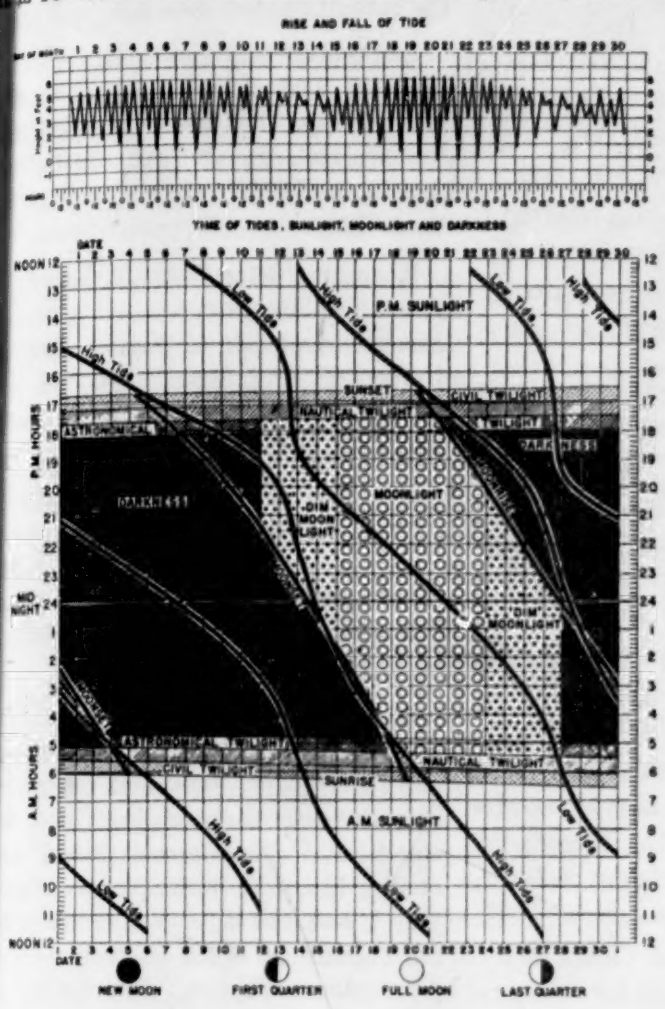

FIG. 2. Tidal illumination diagram for Yokohama, Japan, at time of occupation, November, 1945.

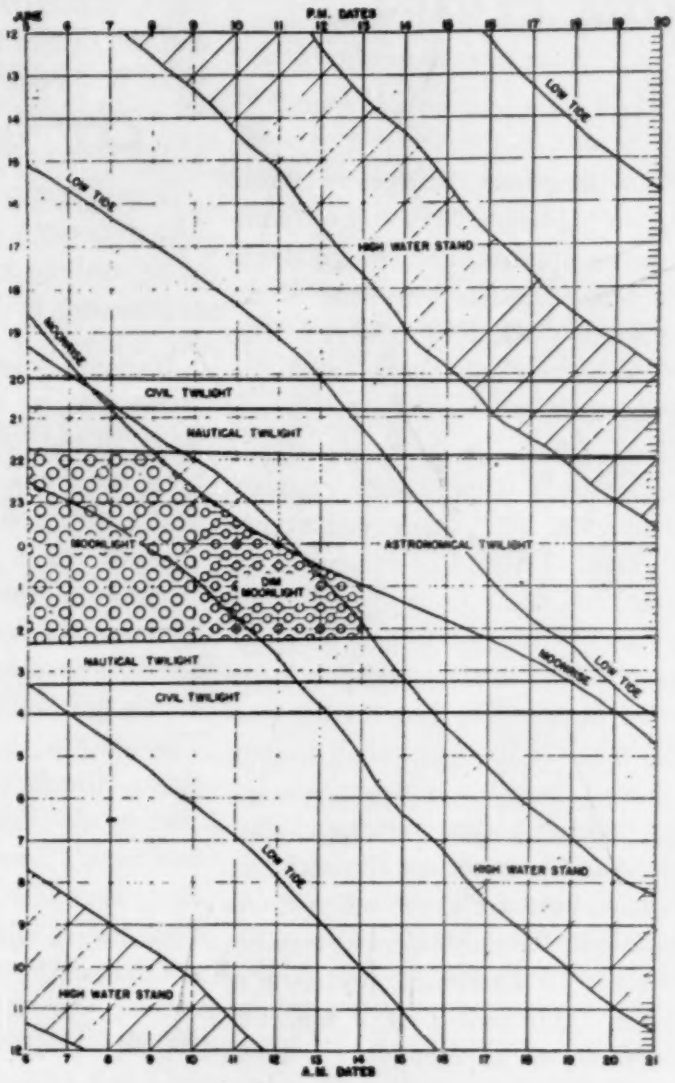

FIG. 3. Tidal illumination diagram for "Omaha" Beach, Normandy, France, during invasion, June 1944.

Tidal illumination diagrams for important target areas of World War II are illustrated by Figs. 2 and 3. These can be prepared for any coastal area where tides have been predicted; their usefulness lies in the prognosis of future conditions as well as in historical studies.

NEWS *and Notes*

"An American Bridge to World Science" (*Science*, May 9, p. 483) outlined the opportunities which might accrue to scientists by virtue of the provisions of the Fulbright Act. This law authorizes agreements with foreign governments for the use of money derived from the sale of surplus property to "finance studies, research, instructions, and other educational activities" of American citizens in the educational institutions of such countries and to transport their own citizens who wish to attend schools in the United States. The law further provides that the President shall appoint a 10-man Board of Foreign Scholarships to select both students and institutions and to supervise the exchange program. Last week such a Board was appointed. The only scientist member is Ernest O. Lawrence, professor of physics, University of California. Others named to membership were: Veterans Administrator Bradley; John W. Studebaker, U. S. Commissioner of Education; Francis Spaulding, New York State Commissioner of Education; Helen C. White, professor of English, University of Wisconsin; Laurence Duggan, director, Institute of International Education; Sarah Blanding, president, Vassar College; Walter Johnson, professor of history, University of Chicago; Charles S. Johnson, president, Fisk University; and Martin P. McGuire, dean, Graduate School, Catholic University. The State Department has already received 12,000 applications for study abroad, 5,000 of these being from veterans.

The $137,550,000 made available thus far is distributed among 22 countries, as follows: Australia, Finland, France, Hungary, and the Netherlands, $5,000,000 each; Austria, $750,000; Belgium, Denmark, Egypt, and Burma, $3,000,000 each; Czechoslovakia, $6,000,000; Greece and Poland, $8,000,000 each; Iran and the Philippines, $2,000,000 each; Italy, China, and the United Kingdom, $20,000,000 each; Netherlands Indies, $7,000,000; New Zealand, $2,300,000; Siam, $4,000,000; and Turkey, $500,000.

Science readers are again referred to "An American Bridge to World Science" and the implications of the Act as presented by William Vogt.

National Science Foundation legislation was, at the beginning of this week, in the hands of conferees from both the House and Senate in order that a compromise might be reached on such issues as appointment of a Director, allotment of research funds to states, and patent provisions. Senate conferees are: Aiken, Ellender, Smith (author of S. 526), Taft, and Thomas; for the House, Harris, Hinshaw, Howell, Priest, and Wolverton (author of H. R. 4102, discussed in last week's issue of *Science*). It seems likely that within a few days a Science Foundation bill will be on its way to the desk of the President for signature.

About People

P. A. Lehenbauer, head, Department of Biology, University of Nevada, has recently retired from that position and is succeeded by **E. W. Lowrance.**

Harold Wooster, University of Pennsylvania, has been appointed senior fellow on the Heinz Food Varieties Fellowship at Mellon Institute.

Iver J. Johnson, professor of agronomy, Iowa State College, has been appointed successor to **H. D. Hughes,** head, Farm Crops Subsection, Department of Agronomy, Iowa State College Agricultural Experiment Station, and head, Farm Crops Subdepartment, Agronomy Department, Division of Agriculture, Iowa State College. Prof. Hughes retired on June 30.

Gilbert H. Ayres, Department of Chemistry, Smith College, has been appointed associate professor in the Chemistry Department, University of Texas. Dr. Ayres will be in charge of analytical chemistry.

Rudolf Bennitt, professor of zoology, University of Missouri, has been appointed visiting professor of zoology at Washington University, St. Louis, for the current summer session.

Ruth McClung Jones, assistant professor of zoology and botany, Swarthmore College, has been appointed professor of biology at Winthrop College, the South Carolina College for Women, Rock Hill.

Norman Foster Ramsey, formerly of Columbia University, has been appointed associate professor of physics, Harvard University. Prof. Ramsey will also continue to serve as consultant to the Brookhaven National Laboratory.

Herman H. Chapman, Harriman professor emeritus of forest management, Yale University, received the honorary D. Sc. degree from the University of Minnesota at its recent commencement exercises.

L. R. Hafstad, director of research, Applied Physics Laboratory, Johns Hopkins University, has been appointed executive secretary of the Joint Research and Development Board, succeeding **Lloyd V. Berkner,** who resigned July 1, and who expects to return in the fall as chairman of the Division of Upper Atmosphere Physics, Department of Terrestrial Magnetism, Carnegie Institution of Washington.

R. E. Black, formerly senior research chemist, Phillips Petroleum Company, Bartlesville, Oklahoma, has been appointed professor and head, Department of Chemistry, Morningside College, Sioux City, Iowa. Prof. Black assumed his duties June 1 after the retirement of **J. A. Coss.**

Hugh Cutler, formerly of the Botanical Museum, Harvard University, and field technician, U. S. Rubber Development Corporation, Brazil, during the war, has been appointed curator of Economic Botany at the Chicago Natural History Museum.

Percy E. Raymond, professor emeritus of paleontology, Harvard University, has been elected a corresponding member of the Geologiska Föreningen, Stockholm.

Ancel Keys, director, Laboratory of Physiological Hygiene, and professor, School of Public Health, University of Minnesota, flew to England July 12

for a two-week series of addresses and conferences. Dr. Keys gave the opening address of the symposium on malnutrition at the International Congress on Pure and Applied Chemistry in London.

W. E. Krauss, head, Department of Dairy Husbandry, Ohio State University College of Agriculture for the past year, will return to the Ohio Agricultural Experiment Station at Wooster as its associate director, January 1, 1948.

David E. Green, director, Enzyme Chemistry Laboratory, Columbia University, has been appointed professor of enzyme chemistry, University of Wisconsin Medical School.

Clarence F. Goodheart, Naval Ordnance Laboratory, White Oaks, Maryland, and **Chester H. Buchanan,** professor and head, Department of Electrical Engineering, University of North Dakota, have been appointed associate professors of electrical engineering, Union College, Schenectady, New York.

Ernest **A. Back,** entomologist, Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, since 1907, retired June 30. On August 1 Dr. Back will leave for London, where, with **R. T. Cotton,** head of the Bureau's Manhattan, Kansas, laboratory, he will represent the Department of Agriculture at the international conference of specialists on infestations of stored products, sponsored by the Food and Agriculture Organization.

Daniel Melnick, supervisor of research, Food Research Laboratories, Inc., has been appointed director, Institute for Applied Research (successor to Applied Research Laboratories, Inc.), Dayton, New Jersey.

W. Henry Hollinshead, formerly professor of anatomy Duke University School of Medicine, has been appointed consultant in anatomy and professor of anatomy at the Mayo Foundation and Graduate School of Medicine, University of Minnesota.

John **E. Anderson,** director, Institute of Child Welfare, University of Minnesota, has been granted sabbatical leave of absence for the year 1947–48. **Dale B. Harris** will be acting director of the Institute during this period.

Harold A. Abramson, assistant professor of physiology, College of Physicians and Surgeons, New York City, and associate physician for allergy, The Mount Sinai Hospital, has been appointed active consulting physician for allergy, Seaview Hospital, Staten Island, New York.

Walter V. Bingham, chief psychologist and adviser regarding the classification of military personnel, War Department, for the past seven years, resigned June 30. Dr. Bingham will serve part time as an expert consultant to the Secretary of War, and as chairman, Council Advisory to the Director of Personnel and Administration, War Department General Staff.

William H. Chambers, chief, Toxicology Branch, **Harold E. Himwich,** chief, Clinical Research Branch, and **Leonard Karel,** toxicologist, represented the Medical Division, Army Chemical Center, at the centenary celebrations of the Chemical Society, London, July 15–17, and the subsequent International Physiological Congress at Oxford.

Warren D. Smith, head, Department of Geology and Geography, University of Oregon, retired on July 1. Prof. Smith is president-elect of the Oregon Academy of Science.

Frederic C. Schmidt, associate professor of chemistry, Union College, has been appointed associate professor at Indiana University, effective September 1. Dr. Schmidt is succeeded at Union College by **Harry F. Herbrandson,** at present a research fellow at Harvard University.

F. C. MacKnight, formerly geologist with The Texas Company, New Orleans, has been appointed professor of geology and geography at Evansville College, Evansville, Indiana.

Raymond L. Taylor, resident head, Department of Biology, Sampson College, Associated Colleges of Upper New York, has been promoted from associate professor to full professor.

Morgan Upton, industrial psychologist, Murray Corporation of Detroit, has been appointed professor, and chairman, Department of Psychology, Rutgers University.

R. E. Buchanan, director, Agricultural Experiment Station, Iowa State College, and **C. H. Werkman,** head, Department of Bacteriology, participated in the 4th International Congress for Microbiology, held this month in Copenhagen, Denmark. Dr. Buchanan helped prepare an international code of bacteriological nomenclature which was presented at the Congress, and Dr. Werkman, one of the principal speakers, discussed cellular metabolism.

Simon H. Ingberg, chief, Fire Resistance Section, National Bureau of Standards, Washington, D. C., has recently retired from this position.

Harry Eagle, Johns Hopkins University School of Hygiene and Public Health, has been appointed scientific director of the National Cancer Institute. Dr. Eagle will have charge of an extensive program of research within the Institute, which is a part of the U. S. Public Health Service.

Henry M. Burlage, professor of pharmacy, University of North Carolina, has been appointed dean, College of Pharmacy, University of Texas, effective September 1, 1947.

David B. Hand, director of research and quality control, Sheffield Farms Company, Inc., has been appointed professor of biochemistry and head, Division of Food Science and Technology, New York State Agricultural Experiment Station, Geneva. Dr. Hand succeeds **Elmer H. Stotz,** who has been appointed professor of biochemistry and chairman, Department of Biochemistry, University of Rochester School of Medicine and Dentistry.

Robert F. Loeb has been appointed Bard professor of medicine in the College of Physicians and Surgeons, and director of the Medical Service at Presbyterian Hospital, according to announcement by Frank D. Fackenthal, acting president, Columbia University, and Charles P. Cooper, president of Presbyterian Hospital. Dr. Loeb has been Lambert professor of medicine at Columbia and attending physician at the Hospital and, during the war, served as consultant to OSRD and chairman of the Board for the Coordination of Malarial Studies. Dr. Loeb succeeds **Walter W. Palmer,** who has become emeritus professor of medicine and consultant of the Hospital.

Edwin R. Whitehead, since last October half-time research professor of electrical engineering and consultant in electrical engineering in general charge of the AC network calculator at Armour Research Foundation, Illinois Institute of

Technology, has been appointed director of the latter's Department of Electrical Engineering. Dr. Whitehead succeeds **Louis T. Rader,** who will join the staff of the General Electric Company.

George H. Young, on the research staff of Mellon Institute since 1935 and executive assistant to the director for the past three years, has been promoted to an assistant directorship of the Institute. During the war Dr. Young was a special consultant on corrosion and protective coatings to the War and Navy Departments.

William W. Ray, associate professor of botany and plant pathology and associatd plant pathologist and mycologist in the Agricultural Experiment Station, Oklahoma A & M College, has been appointee professor of botany at the University of Nebraska, and mycologist in the Department of Plant Pathology of the Agricultural Experiment Station.

Nicholas Polunin, Oxford University graduate and research fellow, has been appointed Macdonald professor of botany, McGill University, to succeed **George W. Scarth,** who has retired.

Ernest H. Ward, formerly professor of psychology, Wittenberg College, Springfield, Ohio, has joined the Los Angeles staff of Rohrer, Hibler & Replogle.

Gleb Krotkov, professor of biology, Queen's University, Kingston, Ontario, is spending his sabbatical leave at the University of California, Berkeley, where he is doing research in carbohydrate metabolism in plants. Mrs. Krotkov is occupying a temporary instructorship in mathematics at Berkeley.

Jessie L. King, chairman, Department of Physiology and Hygiene, Goucher College, Baltimore, retired in June. Dr. King is succeeded as professor of physiology and chairman of the Department by **Phoebe J. Crittenden,** who has been head of the Department of Toxicology, Merck Institute for Therapeutic Research.

John G. Kirkwood, professor of chemistry, Cornell University, has been appointed Arthur Amos Noyes professor of chemistry, California Institute of Technology, effective in September. Dr. Kirkwood is the first to be appointed to this professorship which was recently created in honor of Dr. Noyes, first chairman of the Division of Chemistry.

Arno B. Luckhardt, professor of physiology, University of Chicago, has been designated a distinguished service professor of physiology at the University.

Austin L. Rand, formerly acting chief, Division of Biology, National Museum of Canada, Ottawa, has been appointed curator of Birds at the Chicago Natural History Museum. Dr. Rand assumed his duties there July 7.

H. W. Straley, III, consultant in geology and geophysics, Worthington Consulting Service, since 1940, has been appointed valuation engineer in charge of geological, geophysical, and mining research, World Bank, Washington, D. C.

Jiles W. Haney, chairman, Department of Mechanical Engineering, University of Nebraska, since 1926, will retire as professor emeritus on September 1. **Niles H. Barnard,** formerly associate professor of mechanical engineering at the University, has been named acting chairman.

H. B. H. Cooper, chemical engineer, Calco Chemical Division, American Cyanamid Company, has been named new head of the Department of Chemical and Mining Engineering, Iowa State College, and will assume his new duties early this fall. **O. R. Sweeney,** head of the Department since 1920, will devote his time to research in the Engineering Experiment Station and to teaching in the Department.

Leonard S. Kogan, Psychology Department, University of Rochester, has been appointed assistant director, Institute of Welfare Research, Community Service Society of New York.

P. L. Magill, who has been associated with the DuPont Company for a number of years, has been appointed to the staff of the Stanford Research Institute, where he will direct some of the work in chemistry and chemical engineering.

Visitors to U. S.

Mme. Dobrovolskaia - Zavadskaia, Curie Institute, Paris, plans to attend the Fourth International Cancer Research Congress, St. Louis, Missouri, September 2–7. After the Congress she plans to devote some time to lecturing and conducting scientific discussions on problems connected with "Life and Death Phenomena in Cancerous Cells" and "Possible Role of Some Intermediary Metabolites in Pathology." While in the United States her address will be 2242 Washington Street, San Francisco, California.

Pei-sung Tang, National Tsing Hua University, Peiking, China, wishes to confer with Chinese graduate students in biology, agriculture, biochemistry, and agronomy with a view to possible appointments in China. Dr. Tang will be in this country approximately from August 1 to August 15. Anyone wishing to confer with Dr. Tang is asked to write to him in care of the China Institute, New York City, before August 1.

Members of the South African Council for Scientific and Industrial Research scheduled to visit this country include: J. N. van Niekerk, of the National Physical Laboratory, who arrived July 14; W. S. Rapson, director, National Chemical Laboratory, arriving August 9; E. P. Carman, also of the Chemical Laboratory, arriving August 9; and W. J. Lutjeharms, professor of botany, University College of the Orange Free State, who is traveling on a grant from the Council, arriving sometime in August.

Grants and Awards

Charles Allen Thomas, executive vice-president and technical director, Monsanto Chemical Company, was the recipient of the medal given by the Industrial Research Institute, Inc., of New York City, for "inspiring leadership in the development of the American research system and for the participation thus in the American chemical enterprise." The medal was presented by Herbert W. Graham, senior past president of the Institute, at the annual meeting held June 5 in Swampscott, Massachusetts.

Lawrence H. Bailey, chief engineer, F. J. Stokes Machine Company, Philadelphia, received the annual medal of the Stevens Institute of Technology, June 4, at the third annual medal lecture sponsored by the Powder Metallurgy Laboratory of the Institute. The medal was awarded in recognition of his outstanding achievement in the field of powder metallurgy.

The University of Illinois is to receive $87,850 in Federal Government grants for research and training in the field of psychology. The grants include

$2,000 from the Navy for research in aviation psychology; $4,000 from the U. S. Public Health Service for fellowships, and $7,250 for additional staff; and $44,000 from the Veterans Administration, including income provided by provisions of the G. I. Bill for training in clinical psychology.

The Association for Advancement of Research on Multiple Sclerosis, Inc., has recently made a first grant of $64,350 for specialized research on multiple sclerosis. The three years of research provided for will be under the direction of Elvin A. Kabat, assistant professor of bacteriology, Columbia University. The major part of the project in research in the study of allergies in connection with multiple sclerosis will be conducted at the Columbia University College of Physicians and Surgeons and at the Neurological Institute of New York.

Fellowships

The Arctic Institute of North America is offering two Research Fellowships of $2,000 each for scientific work in the North American Arctic and Subarctic during 1948. Research must include field investigations either in Alaska, northern Canada, Labrador, Newfoundland, or Greenland. The Fellowships are open to anyone who has demonstrated his ability to carry out research work of superior quality in some field of science. Applications must be received by November 1, 1947. Forms may be obtained from The Arctic Institute of North America, 805 Sherbrooke Street West, Montreal, Canada.

The University of Nebraska Foundation has announced the establishment of a geology fellowship by the Shell Oil Company Fellowship Committee of New York City. The fellowship carries a stipend of $1,200 yearly, tuition and fees, and $300 to cover costs of materials and equipment. Recipients will be selected by the chairman of the Department of Geology, with the approval of the dean of the Graduate College.

Colleges and Universities

The University of Michigan has announced the establishment of several distinguished professorships. Among those appointed to these posts were: Werner E. Bachmann, Moses Gomberg professor of chemistry; George G. Brown, Edward DeMille Campbell professor of chemical engineering; Thomas Francis, Jr., Henry Sewall professor of public health; Howard B. Lewis, John Jacob Abel professor of biological chemistry; Dewitt H. Parker, Robert Mark Wenley professor of philosophy; and George E. Uhlenbeck, Henry Smith Carhart professor of physics.

The University of Toledo has announced the establishment of a four-year undergraduate program in glass technology leading to the degree of Bachelor of Engineering. The new program, sheduled to start in September, will be administered by the University's College of Engineering. Clarence L. Babcock, Research Division, Owens-Illinois Glass Company, will have charge of the initial course in glass technology. Further information may be obtained from Walter V. Burg, Department of Chemical Engineering, University of Toledo, Toledo, Ohio.

The Case Institute of Technology has announced the following promotions: Erwin F. Shrader, Department of Physics, to associate professor; Charles S. Smith, Department of Physics, to associate professor; Wiliam A. Lynam, Department of Mechanical Engineering, to associate professor; and Hugh Winn, Department of Chemical Engineering, to assistant professor.

The former University of Newark is now merged with the State University of New Jersey, maintained by the Trustees of Rutgers University. Herbert P. Woodward, formerly professor of geology and acting dean, University of Newark, is now dean, Newark College of Arts and Sciences, Rutgers University; Carl A. Olson, formerly professor of chemistry, is director, Division of Natural Sciences; and John Keosian, formerly associate professor of biology, has been promoted to professor of biology, Newark College of Arts and Sciences.

The University of Chicago has begun construction of a $1,250,000 ion accelerator building to house a 100,000,000-volt betatron, the University's cyclotron, and a new cyclotron of the most modern construction. The laboratory will be used primarily for researches in nuclear physics and radiochemistry conducted by the Institute for Nuclear Studies. Facilities for medical research with high-energy positive ions and gamma rays will be included and used by the Institute of Radiobiology and Biophysics and the Division of Roentgenology of the Department of Medicine in their programs. In this new building, which will be ready for occupancy in the spring, 98 University scientists will conduct basic researches.

Washington Square College, New York University, has announced the following promotions in the Department of Biology: Morris H. Harnly and Douglas A. Marsland to full professor; Albert S. Gordon, Milan J. Kopac, and Alexander Sandow to associate professor; and Savino D'Angelo to assistant professor.

Newly appointed faculty members of the University of Utah School of Medicine include: Emil G. Holmstrom, formerly associate professor in the Department of Obstetrics and Gynecology, as professor and head of the Department to succeed C. E. McLennan, who will become chairman of the Department of Obstetrics and Gynecology at Stanford University; Thomas Dougherty, formerly of Yale University, as professor in the Department of Anatomy; and William Moretz, formerly of Rochester University, as assistant professor in the Department of Surgery, to replace Randolph Shields, who recently left for China.

Swarthmore College has announced the following appointments in the Department of Zoology: Launce J. Flemister, research associate, Sharp & Dohme, Inc., as assistant professor; Jae L. Littrell and Norman A. Meinkoth, Department of Zoology, University of Illinois, as instructors; and Harald Erikson and Valentine Furst, University of Oslo, as research associates.

The Ohio State University Research Foundation has announced the signing of 15 new contracts totaling $428,171 for scientific studies to be conducted at the University for government agencies and industrial firms. Ten of the projects will be carried out for the Army Air Force's Air Materiel Command, the Office of Naval Research, the Cleveland Ordnance District, and the Army Engineer Board, Fort Belvoir, Virginia. Research contracts for the five industrial firms total $107,830. Research for the projects will be conducted in the fields of

fuels, antibiotics, low-temperature research, ceramics and photogrammetry, radio antennae, infrared radiation, aircraft structure design, fungicides and herbicides, poultry husbandry, and criteria for the selection of personnel for positions of responsibility.

Industrial Laboratories

The Sterling-Winthrop Research Institute, a division of Sterling Drug. Inc., will have within a year a new $3,000,000 chemical and biological research laboratory at East Greenbush, New York, near Rensselaer, as the result of an agreement, announced July 12, between Sterling and the Mutual Life Insurance Company of New York. The latter will buy the tract of land from Sterling, finance the construction, and lease the development to Sterling for a 30-year term. Research in the new laboratory will be extended to include "penicillin-like compounds and derivatives, antibiotics, organometallic compounds, sulfa drugs, antimalarials, veterinary products, barbiturates, amino acids, diagnostic agents, streptomycin, and other therapeutic preparations." In the field of tropical medicine, special emphasis will be placed on diseases prevalent in Latin America and the Near East. In addition, research will be undertaken in packaged medicines, fine chemicals, pigments, and dyes.

Eli Lilly and Company announces the appointment to its staff of Joseph Peter Gibbons, Jr., and Darrel O. Neidigh, Jr., both recent graduates of Purdue University.

The Carpenter Steel Company, Reading, Pennsylvania, has announced the appointment of Berton H. DeLong as vice-president and technical director. George B. Luerssen, assistant chief metallurgist, will become chief metallurgist.

Meetings

Brookhaven National Laboratory has arranged several informal conferences on nonrestricted material for August and early September. The dates have been selected to coincide with the visits at Brookhaven of scientists actively interested in the general topics which follow: I. Theory of Nuclear Forces: August 25–29, "Phenomenological Description of Nuclear Structure"; September 2–5, "Nuclear Energy Levels"; September 8–12, "Meson Theory of Nuclear Forces," "Production of Mesons and Protons"; II. Particle Physics: Throughout August, "Cosmic Rays: Composition of Cosmic Rays; Interaction of Mesons With Nuclei; Experimental Techniques"; and "Nuclear Spins and Moments; Interactions Between Nuclear Particles"; III. Instruments of Nuclear Science: August 11-September 12, "Super High-Voltage Accelerators, Theory of Accelerators, Analysis of Power Requirements, Detailed Design Considerations, Uses of High-Energy Particles"; and August 14–15, "Short Pulse Techniques and High-Speed Counters, Crystal Counters, Multipliers and Secondary Emission Phenomena, Cerenkov Counters, Broad Band Amplifiers, High-Speed Coincidence Techniques, Fast Geiger Counters." Information concerning transportation facilities and accommodations may be obtained from Miss Ellen Matteson, Brookhaven National Laboratory, P. O. Box 150, Patchogue, Long Island, New York.

The American Oil Chemists' Society will hold its annual fall meeting at the Edgewater Beach Hotel, Chicago, October 20–22. G. A. Crapple, Wilson and Company, Chicago, is general chairman, and Howard C. Black, Swift and Company, Chicago, is program chairman in charge of technical papers.

Recent Deaths

Grinnell Jones, 63, professor of chemistry, Harvard University, died June 23 at Cambridge Hospital.

Franklin Sherman, 69, head, Department of Entomology and Zoology, Clemson College, since 1925, died of a heart attack June 23.

Frank Clifford Whitmore, 59, research professor of organic chemistry, and dean, School of Chemistry and Physics, Pennsylvania State College, died suddenly, June 24, at his home in State College.

The South African Council for Scientific and Industrial Research has appointed a committee headed by S. H. Haughton, director, South African Geological Survey, to consider how best to organize a marine expedition which would seek to find more living Coelacanthid Fish like that found in the South African waters off East London at the end of 1938, and also to explore and accumulate data in various fields of science in the relatively poorly-known region of the Mozambique Channel. All societies, institutions, and individuals interested in this project are requested to communicate with J. L. B. Smith, Rhodes University College, Grahamstown, South Africa.

The Veterans Administration reference exhibit of prosthetic devices, completed after more than a year's work, was opened to the public on July 16. The exhibit contains approximately 1,000 items, including practically every available known type of device which may aid the physically handicapped. The permanent exhibit may be seen in Room 890, Veterans Administration Building, Vermont and H Streets, N. W., Washington, D. C., 10 A.M. to 4 P.M. Mondays through Fridays.

According to the Swedish-International Press Bureau, the unusual village of Vallhagar, which dates from the middle of the Iron Age and which is located on Gotland Island in the Baltic Sea, will be excavated this summer by about 70 archaeologists from Sweden, Norway, Denmark, Finland, Iceland, and England, who will be aided by geologists, botanists, osteologists, Swedish Air Force photographers, and mine-clearance troops. The object of the excavations is to make a detailed investigation of the settlement in order to determine its design and character. Excavations are expected to be completed by the end of September, and the results will be published jointly by the participating scientists.

The American Society for Research in Psychosomatic Problems has announced the appointment of a new Board of Editors for its journal, *Psychosomatic Medicine*. Carl Binger, psychiatrist, and formerly associate professor, Columbia University, is editor-in-chief. He will be assisted by Franz Alexander, Dana W. Atchley, Walter Bauer, George E. Daniels, Hallowell Davis, David M. Levy, Howard S. Liddell, Milton J. E. Senn, John C. Whitehorn, and Harold G. Wolff.

The U. S. Civil Service Commission has announced an examination for filling Geologist positions at salaries ranging from $4,149 to $7,102 a year. Vacancies are located in Washington, D. C., and vicinity in various Federal agencies, and throughout the United States in the Departments of Agriculture and Interior. Competitors for these positions will not be required to take a written test. To qualify, they must have completed either a four-year college course leading to a Bachelor's degree in geology, or a time-equivalent combination of study in geology and technical experience. In addition, they must have had professional experience in geology. Graduate study may be substituted for a part of the required experience.

Further information and application forms may be obtained at most post offices, from Civil Service regional offices, and from the U. S. Civil Service Commission, Washington 25, D. C. Applications will be accepted in the Commission's Washington Office until further notice, but persons interested in being considered for positions which will be filled immediately should apply by August 15, 1947.

Make Plans for—

American Mathematical Society, First Annual Symposium in Applied Mathematics, August 2–4, Brown University, Providence, Rhode Island.

American Veterinary Medical Association, August 18–21, Cincinnati, Ohio.

New England Association of Chemistry Teachers, 9th Summer Conference, August 18–23, Wellesley College, Wellesley, Massachusetts.

American Pharmaceutical Association, August 24, Milwaukee, Wisconsin.

American Society of Mammalogists, August 24–27, Higgins Lake, Michigan.

Americal Institute of Electrical Engineers, Pacific General Meeting, August 26–29, San Diego, California.

American Association for the Advancement of Science, 114th Meeting, December 26–31, Chicago, Illinois.

COMMENTS
by Readers

So much valuable material is included in Robert M. Salter's paper on "World Soil and Fertilizer Resources" (*Science*, May 23, p 533) that criticism would seem carping were it not that the treatment of the problem is dangerously misleading. It manages to pile up on both the Scylla and Charybdis what the general semanticists call elementalism and identification (Alfred Korzybski. *Science and sanity*, 1933).

It is elementalistic in its isolated discussion of soils, and of fertilizers, which are without meaning, in the world food complex, except as components of the total environment. It overlooks our profound scientific ignorance of how to cope with tropical environments, where only an insignificant amount of research has been carried on. It disregards the illiteracy rate (often 100 per cent) of tropical peoples—and what might be called the ecological illiteracy everywhere of leaders, including legalistic- and "economy"-minded legislative bodies. It begs the question of whether terror-ridden bureaucracies will be able to cope with wind erosion on the chernozem soils of Central Asia. It ignores the instability and corruption of many governments, which seem to exist primarily to line their own pockets.

What of disturbed hydrologic regimes, with their sequelae of floods, drought, falling water-tables, erosion, that have effectively removed from potential circulation millions of acres in Asia, Africa, and South America? What of the burning, overgrazing, overcropping, and deforestation that have made Africa moribund (Jean Paul Harroy. *Afrique, terre qui meurt.* Brussels: Marcel Hayez, 1944)? What of the folkways of Asiatic and African primitives and American pressure groups that measure their wealth in destructive numbers of cattle rather than long-time yields? What of the plague of shifting agriculture that, under increased population pressures, every year sends more millions of tons of soil down the world's rivers, especially those of the tropics? What of the need to resettle hundreds of millions of people already on the land, to give them a decent living standard, and halt erosion? Of what use are millions of tons of fertilizer to India, where 60 per cent of the population has an *annual* per-capita income of $9.30 (S. Chandrasekhar. *India's population*, 1946)? How available are the soils of the tropics, when those who work them face almost certain early death from malaria, dysentery, schistosomiasis, sleeping sickness, and a number of other ills, the control of which is inordinately expensive? What of land tenure systems, tenantry, the colonial and American industrial attitude toward the land, which operates in terms of *this year's* profits? All these factors, it should be borne in mind, are interrelated in a dynamic complex in which it is rare that one does not have an influence on all, or most of, the others.

The paper further suffers from identification of U. S. conditions with those of the rest of the world—it has been done in Iowa; therefore, it can be done in Albania. I have never been in Albania, but I have traveled in many other countries; most of them are decades, perhaps centuries, behind the United States in land use techniques. Not, of course, that we are sitting pretty. We are still losing the battle of soil conservation. We continue to go into the red, from the forest point of view. It is touch and-go whether our western ranges can be saved from the sheep and cattle men. Many of our rivers have been turned into open sewers. Even so, there are few countries outside western Europe that are not far worse off than we.

Meanwhile, the world population is daily increasing at the rate of 50,000 empty stomachs. According to our notions, they should be filled three times a day. It is pleasant to think of 1,300,000,000 available acres and x million tons of fertilizer with which to do it. Unfortunately, for practical purposes, these are as unavailable to hundreds of millions of the earth's people as the gold at the end of the rainbow. And because of man's

unintelligent waste of the soil he is using, and his irresponsible breeding, the marginal lands remaining every year become more marginal.

The problem *can* be solved, but not by resting on a downy bed of false optimism. (WILLIAM VOGT, *2101 New Hampshire Avenue, N.W., Washington, D. C.*)

I agree entirely with Dr. Yerkes (*Science*, May 2, p. 461) in his defense of the scientific status of psychology and the social studies and in his statement that "the scientific method can be applied to all natural *phenomena*" (italics mine); but I think his attack on the *Endeavour* article, as quoted, somewhat confuses the issue. That science can, with sufficient knowledge of the data, predict "whether a picture will have an aesthetic appeal" as a matter of psychological fact to this or that type of observer I do not doubt for a moment; but as to whether the picture *ought* to call forth a favorable aesthetic response, whether it is *deserving* of such a response, science can say nothing; and I think this is really what the author of the *Endeavour* article is chiefly concerned in conveying to his readers. Science is limited to a consideration of what phenomena *are*, but, regarding what *ought* to be, it can say nothing. In other words, all phenomena have a nonphenomenal aspect which scientific method cannot touch, and the values of goodness and beauty to which the author of the article under consideration refers belong to this extrascientific realm. (JARED S. MOORE, *Western Reserve University, Cleveland, Ohio.*)

Alfred E. Emerson has recently pointed out (*Sci. Mon.*, 1947, 64, 343) that human society is largely governed, not by physiological processes (such as are the inherited determinants of activity in a termite society), but by a symbolism that has to be learned. Mathematics, which Bridgman has said is a human invention, is the most significant element in this learning. It can be said to have created science and its results in the industrial revolution that has pyramided the human population of the earth. (See Karl Sax. *Sci. Mon.*, 1944, 58, 66–71.)

Modern society is therefore mathematically conditioned from top to bottom. Nothing that is not mechanical, *i.e.* nothing that does not conform to Lord Kelvin's definition of science as a knowledge arising from being able to "measure what you are speaking about and express it in numbers," can have any bearing on solving social problems. In none of its forms is life mechanistic. But human society, because it is *not* a "living structure," is mechanistic in the character of what Yerkes (*Science*, May 2, p. 462) notes as "this vast array of recent discovery and of technical applications in various branches of human engineering."

Our social problems are therefore coldly intellectual in the detached manner of science. They belong, I suspect, to the cerebrospinal system which is the directive, not the impulsive, autonomic system, with hormones conditioning its reactions. They deal with, but are not themselves, natural phenomena. They are ethical in character, *i.e.* they concern right and wrong as affected by truth and falsehood in what Northrop (*The meeting of East and West*. New York: Macmillan, 1946. P. 442 ff.) calls "epistemic correlations." They are problems, not in observing behavior as if it were conditioned by inherited "ecto-hormones" (Emerson), but in conditioning behavior by institutions which are the locus of the "free will" thus taken over from the individual as he is constrained, by their logic or illogic, into rational or irrational behavior. It is thus not true that (Emerson, *op. cit.*, p. 344) "the problems of human society are much closer to those being solved by the biologists than they are to those of astronomy or nuclear physics."

Whatever psychology may have accomplished or failed to accomplish is irrelevant socially if it is dealing with natural phenomena under hereditary stimuli. Therefore, a "lack of faith in the applicability of scientific procedures to psychological and social phenomena" is warranted (*contra* Yerkes, *op. cit.*, p. 462), because social phenomena are not natural, *i.e.* they are not psychological, but are intellectual. And intellectual controls are not real, natural phenomena but are ideal, purposive inventions, with social objectives, which may or may not be rational, *i.e.* suited to their purpose.

Any organism can make a bad, even a fatal, choice. But when "all we like sheep have gone astray," we have done it by *thinking* blindly *before* acting blindly, in concert. So, human cooperation is not necessarily beneficent, as is implied by current diplomatic palaver. An irrationally conditioned society cannot promote beneficent cooperation merely because its individuals or leaders wish to do so. Their logical, not their psychological, directives determine the nature of events; and the events do not contain their own causation as in natural phenomena. If they did, prayerful thinking would be quite in order and would be correctly fatalistic.

The historical materialism that is shaping the *ir*rationale of the current institutional developments of "socialism" is irrational in its interpretations because it believes, as does Dr. Yerkes (*op. cit.*, p. 461) that "the scientific method can be applied to all natural phenomena" and that social phenomena are natural in their sequences. That this is not true is the central theme presented by Northrop (*op. cit.*, p. 255 ff.) in protesting against the culturalistic fallacy of trying to derive a normative theory from the factual theory of social "science."

Thus, the "hosts of us who are now classified as scientists" may well be "self-deceived workers who, unlike our physical science colleagues, are denied access to the truth concerning the natural phenomena which particularly interest us" (Yerkes, *op. cit.*, p. 462)—because they simply are not natural phenomena! The social psychologist, arbitrarily placing all events in the natural field, destroys the realistic epistemological dualism in philosophy upon which an effectively integrated science depends.

"Culturology" (see L. White. *J. Wash. Acad. Sci.*, 1947, **37**, 181–210) may well serve as an escape from the egocentric predicament of the personal, psychological approach to social problems; but it seems certain that its rationale can only be, not that of a new empiricism, but simply the timeless metaphysical disciplines of philosophy and logic. We shall come to see mathematics as a cultural artifact or "human invention." As such, it represents a social device for choosing, not ends, but means; nor is it an "illusion of omnipotence" to recognize it as the ultimate in social recourses. Its logic is, indeed, compelling; but who would say that the laws of reason are as unbreakable in human society as are the laws of motion in the "infinite meadows of heaven"? Truth is not a robot! (ALDEN A. A. POTTER, *R.F.D. 3, Bethesda, Maryland.*)

TECHNICAL PAPERS

Reproductive Cycles of Five Species of Texas Centrarchids[1]

CLARENCE L. SCHLOEMER

Basic College, Michigan State College, East Lansing, Michigan

During 1941 and early 1942 data were taken from approximately 2,350 centrarchids from a group of 5 artificial lakes located in eastern Texas. The lakes, owned by a private hunting and fishing club, ranged in size from 75 to 650 acres. The species studied were the largemouthed black bass, *Huro salmoides* (Lacépède); the white crappie, *Pomoxis annularis* Rafinesque; the black crappie, *Pomoxis nigro-maculatus* (LeSueur); the bluegill, *Lepomis macrochirus* Rafinesque; and the redear sunfish, *Lepomis microlophus* (Günther). In this report attention is given to the reproductive cycles of the 5 species between March 1941 and March 1942. Restrictions on travel caused by the war terminated the research program at that time.

TABLE 1

OVARY WEIGHT/BODY WEIGHT RATIOS × 10^3 (GRAMS) FOR 5 SPECIES OF CENTRARCHIDS IN TEXAS DURING 1941 AND EARLY 1942

Date	Species				
	Large-mouthed bass	White crappie	Black crappie	Bluegill	Redear
Mar. 23	32.9 (9)*	56.2 (33)	61.0 (11)	— —	27.5 (4)
Apr. 6	33.8 (13)	29.3 (7)	44.3 (4)	30.3 (3)	62.6 (15)
" 20	30.8 (4)	25.2 (5)	14.3 (3)	41.0 (3)	69.1 (13)
May 10	9.7 (13)	5.9 (15)	5.5 (8)	28.3 (8)	26.8 (9)
" 31	3.8 (4)	— —	4.3 (7)	30.9 (8)	21.3 (7)
June 21	4.2 (9)	2.8 (10)	3.3 (4)	22.4 (5)	17.9 (18)
July 19	3.5 (4)	3.0 (1)	2.6 (3)	19.7 (13)	5.8 (13)
Aug. 29	2.4 (16)	2.5 (5)	2.8 (20)	14.6 (20)	5.0 (13)
Oct. 5	3.6 (7)	4.5 (9)	4.2 (21)	— —	— —
" 31	1.9 (2)	— —	— —	— —	— —
Nov. 18	2.4 (11)	— —	— —	— —	— —
Jan. 24	11.5 (26)	17.3 (14)	25.5 (15)	9.0 (2)	11.1 (11)
Mar. 1	8.3 (2)	— —	— —	14.4 (3)	14.4 (4)
" 18	21.5 (2)	28.1 (2)	40.7 (1)	5.6 (2)	11.6 (4)
" 28	38.6 (12)	— —	— —	22.8 (4)	49.5 (11)

* Figures in parentheses indicate frequencies.

All the data upon which this study is based were taken from fish caught by the club members and included material essential to the study of food habits and age and rate-of-growth determinations, as well as the reproductive organs. The viscera were preserved in a 5 per cent solution of formaldehyde. At a later time the ovaries were weighed to the nearest .1 gram, and the ratio of ovary weight/body weight multiplied by 10^3 was determined for 525 individuals. These ratios and the frequencies arranged according to the date of collection are presented in Table 1.

When presented graphically, as in Fig. 1, several interesting points are brought out with respect to the reproductive cycles of the species considered. If it is assumed that the period covered by the decline in the slope of the curve represents the spawning period for each species, considerable variation in the length of the spawning periods is evident. The bluegill population, for example, spawned well into September after reaching a peak of gonadal development around April 20. The largemouthed black bass, on the other hand, spawned from the middle of April until the end of May. The white and black crappie populations spawned from the latter part of March until the early part of May, while the redear sunfish held an intermediate position among the populations, the spawning period extending from around April 20 to the end of July. Expressed in terms of spawning intensity, it is also evident that in 1941 the maximum decline in the value of the ovary weight/body weight ratio for the bass, redear sunfish, and bluegill populations occurred approximately one month after the crappie populations showed their maximum decline in the value of the ratio. The mean air temperatures during the months of March and April in this locality were 53° and 67°F., respectively.

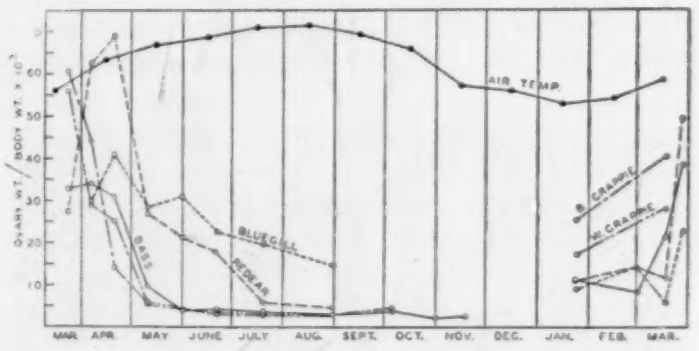

FIG. 1

Fig. 1 also indicates that the ovary weight/body weight ratio remains at a low level for several months, followed by a gradual and then abrupt increase in value. For example, in the largemouthed black bass population the ratio dropped from 30.8 in late April to 3.8 in the latter part of May and remained approximately at this level until the middle of November, beyond which point no data were available for 1941. The next collection, however, showed an increase in the ratio from the November low of 2.4 to the January level of 11.5, and an abrupt increase occurred during the month of March, when a high of 38.6 was attained. This abruptness in gonadal development was also evident in the redear sunfish population in both 1941 and 1942. The collections of January and March in 1942 also show the crappie populations to be ahead of the other species in ovary development. The

[1] Contribution No. 14, Department of Biological Science, Michigan State College. The fishery program of which this study is a part was made possible by the cooperation of the Koon Kreek Klub and North Texas State College. The author also acknowledges the assistance of R. Bagwell and J. M. Faggard.

mean monthly air temperatures for the first three months of 1942 were 46°, 49°, and 58° F., respectively.

Studies such as this, if carried on over an extended period of time to determine the degree of variation which undoubtedly exists in the length of the spawning periods, the periods of maximum decline in the ovary weight/body weight ratios, and the causes of such variation, would assist materially in providing a more scientific basis for the establishment of "closed seasons" if the evidence justified restrictive fishing measures.

Intercellular Surface Phagocytosis[1]

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Pathogenic microorganisms with protective capsules are ordinarily considered resistant to phagocytosis unless previously opsonized by specific antibody (*1*). Evidence has recently been presented that both encapsulated pneumococci (*3, 4*) and Friedlander's bacilli (*2*) are readily phagocyted in the absence of antibody by a mechanism referred to as surface phagocytosis. Direct visualization of this nonantibody form of phagocytosis in the lung has shown that the leucocytes phagocyte the encapsulated bacteria by trapping them against the surface of the tissue. Once taken into the cytoplasm of the phagocytic cells, the bacteria are rapidly killed (*2, 4*).

During experiments in which surface phagocytosis of Friedlander's bacilli in lung sections was being observed directly, phagocytosis was occasionally noted at some distance from the alveolar walls. The phagocytosis occurred whenever bacilli happened to get caught between the surfaces of two or more colliding leucocytes. On such occasions the surface of the adjacent leucocyte appeared to act in the same capacity as did the alveolar wall in the previously described form of surface phagocytosis. When the number of leucocytes in the phagocytic mixture was increased, the intercellular surface phagocytosis was noted frequently (see Fig. 1).

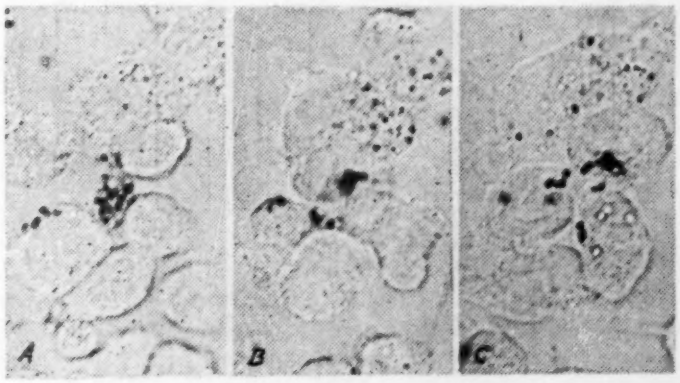

Fig. 1. Intercellular surface phagocytosis: (A) Leucocytes surrounding a group of encapsulated Friedlander's bacilli in a medium devoid of antibody (time, 2:10 P.M.); (B) Leucocytes have closed in on the bacilli so that they are trapped between the surfaces of the phagocytic cells (time, 2:23 P.M.); (C) The trapped bacilli have been phagocyted and can be seen in the cytoplasm of three of the leucocytes (time, 2:40 P.M.).

From these direct observations it appeared likely that intercellular surface phagocytosis would result whenever the concentration of leucocytes became such that the encapsulated bacteria could be readily trapped between two or more cells. To test this hypothesis, the following experiment was performed:

Friedlander's bacilli harvested from 2 ml. of a 4-hour broth culture (*2*) were suspended in gelatin-Locke's solution along with washed leucocytes obtained from the peritoneal cavities of 4 rats previously injected with starch aleuronat (*2*). The leucocyte-bacillus mixture was then concentrated by centrifugation (2,000 r.p.m. for 5 minutes), and as much supernatant fluid as possible was removed with a pipette and discarded. The concentrated mixture, which now contained a minimum of free fluid, was incubated for 30 minutes at 37° C., and smears of the mixture were stained with methylene blue. Examination of the smears revealed marked phagocytosis of the Friedlander's bacilli, whereas in control experiments, in which the leucocyte-bacillus mixture was not concentrated, little or no phagocytosis resulted.

Similar results were obtained with *Pneumococcus* Type I (A5 strain), *Pneumococcus* Type III (A66 strain)[2], and a mouse-virulent strain of *Staphylococcus aureus* (strain 235). Young cultures of each of these organisms resisted phagocytosis when incubated with leucocytes in dilute solution.

Intercellular surface phagocytosis of a number of pathogenic encapsulated organisms was thus brought about merely by diminishing the amount of fluid in the bacteria-leucocyte mixtures. Although the capsules protect the organisms against phagocytosis when the bacteria are floating freely in a fluid medium, they fail to protect them against surface phagocytosis when the latter occurs on a tissue surface or as a result of the intercellular mechanism just described. As previously stated, bacteria ingested by the nonantibody mechanism of surface phagocytosis are promptly killed by the phagocytic cells (*2, 4*).

The significance of intercellular surface phagocytosis in the mechanism of recovery in pneumococcal and Friedlander's bacillus pneumonias is indicated by the following considerations:

Although the earliest reaction of the lung to acute bacterial infection is the outpouring of edema fluid into the infected alveoli, this first stage is promptly followed by a rapid accumulation of leucocytes at the site of infection. The amount of edema fluid in the alveoli and bronchi diminishes, and the number of leucocytes present increases until the phagocytes are so numerous that they form the solid mass of cells characteristic of the advanced stages of pulmonary consolidation. Such a concentration of phagocytic cells eventually makes it virtually impossible for bacteria in the consolidated areas to escape surface phagocytosis. Those organisms that are not trapped against the tissue surfaces of the alveoli and bronchi are eventually phagocyted by being pinned between the surfaces of two or more of the crowded leucocytes. Thus, leucocytes in the lung may, through these two forms of surface phagocytosis, bring about destruction of even the most virulent encapsulated organisms, in the complete absence of immune bodies.

Conclusions: Encapsulated bacteria are phagocyted by leucocytes in the absence of opsonins, not only by being trapped against tissue surfaces but also by being caught between the surfaces of the phagocytic cells. Because large num-

[1] These studies were supported by the Commonwealth Fund.

[2] Kindly supplied by Colin M. MacLeod, of New York University.

bers of leucocytes accumulate in the lung during acute bacterial pneumonia, it is concluded that intercellular surface phagocytosis causes the destruction of many of the invading organisms, particularly during chemotherapy in the early stages of the disease when specific antibodies are not present to opsonize the bacteria.

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Use of 2,4-D Weed Killers on Woody Weeds in Cuba

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The problem of eradication of woody perennial weeds is much more serious in the tropics than in temperate zones. In Cuba the most serious weed is the legume *Dichrostachys nutans*, known as *Aroma marabu*. Since this plant regenerates vigorously from cut stumps, its eradication by continued cutting is almost impossible. In experiments carried out at the Atkins Garden and Research Laboratory of Harvard University, at Soledad, Cuba, several preparations and methods of spraying of 2,4-D have been tested on plots of large, well-established plants from cut stumps. Although delayed regeneration is still not entirely excluded, the following approximate figures for apparent kills in 4 weeks have been obtained:

TABLE 1

Treatment	Per cent apparently killed	Per cent probably alive
1. 2,4-D sodium salt, 0.2%	18	21
2. The same applied twice, 5 days apart	76	8
3. The same, 0.3%, applied once	62	8
4. The same, 0.3%, plus Carbowax 1500, 0.5%, applied once	87	1
5. 2,4-D ester, 0.3%, applied once	94	4

Since the plants die slowly, the percentage kill increases steadily with time, and a number of plants have to be classed as doubtful for a month or more after treatment. On balance, treatment No. 4 was considered the most effective, although No. 5 gave the most rapid defoliation. The volumes used were about 100 gallons/acre.

Plants in the shade were only slightly less affected than those in the sun. Spraying on the underside of the leaves did not increase the toxicity.

Another troublesome plant, *Comocladia dentata* (Guao), having a toxic action on the skin like that of poison ivy, was also studied. In this case the ester preparation ("Weedone") was definitely more effective than either the salt or the free acid, probably because of its better adherence to the vertical glossy leaves, from which aqueous sprays ran off rapidly. A concentration of 0.3 per cent gave about a 75 per cent kill as determined 6 weeks after spraying.

These experiments, which give promise of possible reclamation of land up to now considered virtually unavailable, are being continued.

Note on the Theory of Radiation-induced Lethals in *Drosophila*

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A rather complete theory of induced lethals in *Drosophila* which was proposed by Lea and Catcheside (*5*) has met with objections in private discussions. As this theory is now embodied in a comprehensive book (*4*) (reviewed in *Science*, April 25, p. 454), it may be advisable to publish some comments on the matter.

The frequency of x-ray–induced, sex-linked recessive lethals in *Drosophila* is experimentally known to be accurately[1] proportional to the x-ray dose, at least up to about 5,000 r. The presence among these lethals of a large number which are located at points affected by chromosomal rearrangements creates a well-known difficulty for the interpretation of the dependence of frequency on dose (*2*). If it is simply assumed that this fraction of lethals is a by-product of the rearrangements, the total frequency of recessive lethals should increase faster than in proportion to the dose. Lea and Catcheside made the alternate assumption that the recessive lethals and the rearrangements result independently from a single type of primary effect. This primary lesion, the frequency of which is assumed to be proportional to the dose, may or may not, according to chance, lead to a recessive lethal and/or to a rearrangement. Such a common ancestry accounts for the observed coincidence of recessive lethals with rearrangements. It must also cause, however, a parallel frequent coincidence between the recessive lethals and those rearrangements (e.g. dicentrics) which are unviable ("dominant lethals") and thus escape detection. The latter rearrangements thus make an inroad in the observable recessive lethals, which should become increasingly important with increasing dosage; consequently, the frequency of recessives should increase slower than in proportion to the dose.

This nonlinear effect, embodied in Lea and Catcheside's detailed theory, leads to a very significant discrepancy between this theory and the experimental data. The authors merely discount the discrepancy because they reckon on having overestimated it by an undetermined amount (*5*). It is proposed here to give a minimum estimate of the importance of this discrepancy, using general arguments.

Lea and Catcheside classify the recessive lethals as class *A* (associated with no rearrangement), class *B* (associated with a minute rearrangement), and class *C* (associated with a viable gross rearrangement). This latter kind of rearrangement will be called *VGR*. We shall also consider class *D* lethals, *i.e.* those associated with an unviable gross rearrangement (*LGR*).

The various symbols will be used to indicate the corresponding frequencies, but it should be noted that the frequencies of *C*'s and *VGR*'s *among viable sperms* are, respec-

tively, $C/(1-LGR)$ and $VGR/(1-LGR)$. The Lea-Catcheside assumption means that $A+B+C+D$ is proportional to the x-ray dose; the frequency of recessive lethals among viable sperms is $A+B+C/(1-LGR)$. The departure of these two expressions from one another, which is a measure of the nonlinear effect, can be expressed as:

$$\frac{A+B+C+D}{A+B+C/(1-LGR)} - 1 = \frac{D - C\,LGR/(1-LGR)}{A+B+C/(1-LGR)} = \frac{C/(1-LGR)}{A+B+C/(1-LGR)} [(D/C)(1-LGR) - LGR]. \quad (1)$$

The first factor in the last expression is the fraction of C's among the observable lethals. The bracketed factor can be reduced by algebraic manipulation to a form involving only the experimentally known frequency $VGR/(1-LGR)$ and factors on which predictions can be made. These are $p = LGR/VGR$ and $q = \frac{D}{LGR}/\frac{C}{VGR}$. The quantity (1) can then be written as

$$p\,\frac{q - VGR/(1-LGR)}{1 + p\,VGR/(1-LGR)} \quad \frac{C/(1-LGR)}{A+B+C/(1-LGR)}. \quad (2)$$

As stated above, $\frac{C/(1-LGR)}{A+B+C/(1-LGR)}$ and $VGR/(1-LGR)$ are observable quantities which, at 3,000 r, amount to about 1/3 and 1/5, respectively (*4*). The factor $p = LGR/VGR$ would be 1 if every rearrangement involved only two breaks; since this is not so, p will in general be larger than 1 (*2*) and might be even as large as 2 at 3,000 r. The factor $q = \frac{D}{LGR}/\frac{C}{VGR}$ would also be 1 if *VGR*'s and *LGR*'s had the same chance of being associated with a sex-linked recessive lethal; actually, $q > 1$, since the *LGR*'s are expected to have more breaks, on the average, than the *VGR*'s. The quantity (2) is thus certainly larger than the value found by taking $p = q = 1$, which at 3,000 r would be about 2/9. For $p = 2$, $q = 1$, it would be 8/21.

Therefore, it can be stated that the nonlinear effect amounts to at least 20–25 per cent at 3,000 r. On the assumption that the *C* lethals are by-products of *VGR*'s the nonlinear effect is $(A+B)/(A+B+C) - 1 = C/(A+B+C) = 1/3$—that is, possibly a somewhat larger one. The Lea-Catcheside theory may thus reduce the nonlinear effect by a factor which amounts to 1.5 at most. The remaining nonlinear effect is probably significantly at variance with the set of experimental data discussed by them. At any rate, it seems quite unlikely that an effect of such quantitative importance could have failed to be detected in all the extensive studies on this subject by so many different workers.

It may well be that the Lea-Catcheside concept of the recessive lethals, as manifestations of the same type of primary lesion which leads to the observable chromosomal breaks, is essentially correct. But the process of x-ray–induced breakage and recombination in *Drosophila* has thus far defied not only a quantitative but even any comprehensive qualitative analysis (*2*, *3*). This difficulty may well prevent for the time being any satisfactory account of the relationship between recessive lethals and rearrangements and of their dose-frequency relationships. This same difficulty, incidentally, seems to put the Lea-Catcheside detailed calculation of the dose-frequency relationship for dominant lethals (*4*, *5*) on a very doubtful ground, although there seems to be no difficulty with the qualitative understanding of this relationship.

A final remark may be added concerning the recessive lethals (*B*) associated with minute rearrangements. Lea suggests that the deficiencies involving several salivary chromosome bands are due to separate breakage processes caused by a single ionizing particle, in analogy to the mechanism which he successfully proposed for *Tradescantia*. However, the frequent occurrence of spontaneous lethals involving deficiency of several bands (*1*) suggests that such deficiencies are the outcome of a single primary, probably much more closely localized, lesion. The larger deficiencies up to about 50 bands, and the corresponding minute inversions, are generally accepted to be due to the same mechanism as the *VGR*'s (*4*). Accordingly, a substantial fraction of the class *B* recessive lethals should have been transferred to class *C* for the purpose of the calculation carried out in this paper; this would have made the nonlinear effect appear even more important.

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Cosmic Radiocarbon and Natural Radioactivity of Living Matter

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In view of the discovery of radiocarbon produced by cosmic radiation (*1*), it becomes of interest to compare its effect in living matter with that due to the older sources of activity, such as radium and its decay products, or potassium, and to the action of cosmic rays. Since data on humans are most readily available to us, we will limit ourselves here to a comparison *in man*.

This comparison can be made on various bases, such as range, ionizing power, or total energy of the particles. The range varies from the extremely small range of α-particles up to the whole length of the human body for cosmic rays. The ionizing power per unit length varies in reverse order and decreases from the higher value for α-particles to cosmic rays.

As radiochemists, it seems to us that the simplest basis of comparison would be the number of disintegrating atoms (or

rays) per human being and per unit time. Table 1 shows a preliminary comparison based on an estimated average body weight of 80 kg.

TABLE 1

Element	Wt. % in human body	Total element in body (grams)	Literature source	Specific act. dis./min. and 1 gram element	Nature of emitted particle	Dis./min. and man
Potassium	0.35	280	Sherman (2)	1,340	β	380,000
Carbon	18.0	14,400	"	10.5	β	150,000
Radium	$\approx 10^{-12}$	$\approx 8 \cdot 10^{-9}$	Vernadsky (3)	$2.22 \cdot 10^{12}$	α	$\approx$18,000
	$\approx 5 \cdot 10^{-13}$	$\approx 4 \cdot 10^{-9}$	Evans*	"	α	$\approx$9,000

*Private communication from Robley D. Evans, Massachusetts Institute of Technology

The intensity of cosmic radiation at sea level corresponds to approximately 1 meson per minute and per cm.^{2} Therefore, depending on whether the human being is in a standing or lying position, *i.e.* on his "cross section," the number of penetrating particles ranges approximately between 1,500 and 7,500 per man and per minute.

Thus, comparing these data, we see that cosmic radiocarbon occupies second place. Based on number of disintegrations, it is a little below half of potassium, but very much above radium and other natural radioelements. Only because of the low *specific* activity of carbon has it escaped detection so far. We believe that the biological significance of the radioactivity of carbon in living matter cannot be evaluated in physical terms alone; specific biological and biochemical factors may also play a role. It will be up to future research to establish these.

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IN THE LABORATORY

Bioassay by Direct Potency Estimation[1]

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Two main approaches are used to determine the potency (Py) of a drug, *i.e.* the ratio between threshold equipotent doses of the standard (S) and the unknown drug (U) (Py = S/U). One procedure uses the median effective doses (ED_{50}) of standard and unknown as expressions for S and U, respectively, and operates by determining these two values in separate populations of test animals. Another assay method compares the standard and the unknown drug on the same test object or animal. Usually the aim is first to find in each of various test individuals a pair of equipotent doses of the standard and the unknown ($s^1, u^1; s^2, u^2; s^3, u^3$; etc.) each such dose level complying with a set end-point in a critical range of effect, and then to obtain from these dose pairs a number (N) of equality statements (E), each E representing an estimate of the intraindividual potency in the respective test object ($E^1 = s^1/u^1$; $E^2 = s^2/u^2$; $E^3 = s^3/u^3$; etc.). Py is then defined as the average of the intraindividual potencies $\left(\frac{\Sigma E}{N}\right)$. Thus, in the latter method, potency is evaluated directly on the basis of intraindividual potency statements and not by a preceding determination of S and U which is characteristic of the former method. The former may therefore be called an indirect, and the latter a direct, method of potency evaluation.

The indirect method does not need any special biostatistical basis. Determinations of ED_{50} have long been placed upon an elaborate mathematical basis, and their adoption has satisfied all biostatistical requirements of such a method. On the other hand, the direct method has two major shortcomings: It lacks a rigorous biostatistical means for defining the significance of the result, and its purpose is accomplished in an uneconomical trial-and-error procedure. Prior to arriving at the respective doses s and u, one has to perform tests with a varying number of doses either higher (h) or lower (l) than s or u, respectively, *i.e.* with doses h_s and l_s of the standard and doses h_u and l_u of the unknown. The data from all these preliminary tests are ultimately discarded as being "aberrant."

Only in one variant of direct procedure, the "method of approximation" (*2*), are these aberrant doses utilized for obtaining a rough estimation of the significance of the result. They are paired, both mutually and with the respective s and u values, to form additional statements pertinent to potency, namely, statements H of maximum potency (signifying Py < H), expressed by the ratios h_s/l_u, s/l_u and h_s/u, and statements L of minimum potency (Py > L), expressed by the ratios l_s/h_u, s/h_u and l_s/u. All these H and L values are then arranged in

[1] Experiments underlying this paper were in part supported by grants-in-aid of research from the U.S. Public Health Service and the Abbott Laboratories.

numerical progression; they approximate the true Py value from opposite directions, and the range of overlap indicates the deviation from the true Py. For example, the series of experimental H, L, and E data in columns 1 to 3 of Table 1 would indicate a mean Py of 27.2 and a deviation of ±16.5 (or ±45 per cent) from a midvalue of 36.5.

TABLE 1

POTENCY ESTIMATION OF THE 3-(1-METHYL-OCTYL) ANALOG OF SYNTHETIC TETRAHYDROCANNABINOL*

1	2	3	4	5	6	7	8	9	10
H	E	L	n_H	n_E	n_L	M Py of group	$n_H+n_E+n_L$	λ_H	Probit
60									
60			3	0	0				
60						56.0	6	5.5/6	6.37
52	52		2	1	0				
52									
50	50								
50	50		2	2	0				
48									
48			3	0	0				
48						46.8	13	9/13	5.50
46	46								
	46		1	2	0				
	42	42							
	42		0	2	1				
40	40	40	1	1	2				
		40							
	36.4		0	1	0				
34		34	1	0	2				
		34							
33.6			1	0	0	32.9	17	9/17	5.15
33.4	33.4		1	1	0				
		33.2	0	0	1				
32	32	32	2	1	1				
32									
30.8			1	0	0				
	30	30	0	2	1				
	30								
	27	27	0	1	1				
		25.2	0	0	1	26.2	10	2/10	4.16
	24	24	0	1	1				
		23.4	0	0	1				
		21.2	0	0	1				
	20	20							
	20	20							
		20	0	2	5				
		20							
		20				18.4	11	1/11	3.51
		18	0	0	2				
		18							
		16	0	0	2				
		16							

N = 57

$2s' = 50.8 - 23.6 = 27.2$

$\sqrt{2N'} = 10.68$

Py = 35.0

s.e. $= \frac{2s'}{\sqrt{2N'}} = \pm 2.54$

* Test function: ataxia activity in calibrated dogs.
Standard: synthetic tetrahydrocannabinol.

Even in this variant, the direct bioassay procedure is mathematically unsatisfactory, and preference is given whenever possible to the indirect method. Yet, of necessity, the direct method is employed whenever the test objects (e.g. isolated organs, monkeys, dogs) are from populations with excessive interindividual variation or whenever intraindividual comparison is the procedure of choice. This signifies a wide field of actual use of, and too great a need for, procedures for direct Py estimation to dismiss them summarily as devoid of mathematical background (*1*) rather than to furnish constructive assistance for their improvement.

Obviously, conventional biostatistical methods can readily be applied to the data from such intraindividual dose comparisons. The totality of data on maximum, intraindividual, and minimum potency, collected for the above procedure of approximation, furnishes useful information, and the alignment of such data in a series of approximation (compare Table 1, columns 1 to 3) offers an appropriate starting point for a statistical likelihood solution.

The likelihood λ_H that any of the tentative potencies expressed by H or L values or both is greater than the true Py varies along the approximation series. If the total range is subdivided into appropriate groups of tentative potency, the likelihood that the mean Py of the individual group (M Py = $\frac{\Sigma H+\Sigma E+\Sigma L}{n_H+n_E+n_L}$) is greater than the true potency value Py is expressed by the proportion between the number of H statements (n_H) and the total number of potency statements ($n_H+n_E+n_L$) available for the group. The ambiguous E values must be assumed to express an equal likelihood that the median Py value of the group is too high and that it is too low. Accordingly, the final likelihood for a group is $\lambda_H = \frac{n_H+n_E/2}{n_H+n_E+n_L}$. The λ_H values coordinated to each M Py are calculated and converted into probits by reference to a probit table or to a table of integral of the normal probability curve. The probits, when plotted against the logarithm of their M Py, approximate a straight line. The abscissa value of the intersection of this line with the probit ordinate of 5 is an estimate of the true potency Py having a λ_H of 0.5. The standard error (s.e.) may also be determined from the same graph according to the formulation s.e. $= \frac{2s'}{\sqrt{2N'}}$, where 2s′ is the difference between the abscissa values of the intersections of the experimental line with the probit ordinates of 4 and 6, and where N′ is the number of potency statements within the range of probits 3.5 and 6.5.

The total procedure is illustrated by the example in Table 1, in which the biostatistical evaluation is shown applied, in parallel with the "method of approximation," to the same experimental data. Fisher's probit table and a graphical interpolation procedure comparable to that of Miller and Tainter (*3*) were employed after calculation of the M Py and λ_H values. The Py value obtained differs greatly from that computed by the "method of approximation," and the s.e. is much smaller than the range of deviation in the series of approximation. It should also be mentioned that the good agreement between the roughly computed midvalue of Py and the mathematically estimated Py value is merely accidental and that frequently there is considerable divergence between the results of the approximation method and those of the method herein outlined.

The suggested procedure for direct potency estimation has been found expedient in numerous bioassay problems, e.g. in

assaying spasmolytic and antihistaminic drugs in isolated strips of surviving gut; laxatives in terms of stool softening in rhesus monkeys; marihuana-active substances in terms of ataxia in dogs; and sympathomimetic agents in terms of ability to elevate the cat's blood pressure. The task of assaying biological activity by intraindividual comparison is not limited to drugs, but arises in many cases in which the potency of commensurable stimuli—agents, factors, etc.—has to be correlated numerically on the basis of a common response. It is believed that the principles of this procedure may be serviceable in various disciplines other than pharmacology.

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Identification and Chromatography of Androgens as Their 2,4-Dinitrophenylhydrazones

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Frequent use is made of 2,4-dinitrophenylhydrazine (DNPH) for the characterization of aldehydes and ketones, and the chromatographic adsorption of a number of the hydrazones of DNPH is described by Strain (*2*). However, the reagent does not appear to have been widely used in the study of steroid ketones. Veitch and Milone (*3*) have published a method for the estimation of estrone as the 2,4-dinitrophenylhydrazone, but their procedures seem not to have been applied to androgens. These studies suggested the possibility of using DNPH for the isolation and characterization of the constituents of commercial androgen preparations. In 1941 Coffman (*1*) reported the preparation of several androgen esters of p-phenylazobenzoic acid and was able to resolve mixtures of several of these colored esters chromatographically. In dealing with commercial products, however, this type of derivative could not be expected to distinguish between free and esterified androgenic steroids.

This paper constitutes a preliminary report of the preparation and properties of the DNP-hydrazones of testosterone, testosterone propionate, methyl testosterone, androsterone, and dehydroisoandrosterone. First attempts to prepare the hydrazone of one of these androgens (testosterone propionate) directly in an oil solution indicate that such a procedure is possible and may be developed into a useful analytical method. Over-all yields of about 60 per cent have been obtained to date. Details will be published as soon as the techniques are perfected.

The chromatographic separation of mixtures of some of these hydrazones has been accomplished, which indicates the possible application of the reagent to urinary extracts of ketosteroids for investigations in androgen metabolism.

[1] Thanks are due Mrs. Doris C. Chambers, of the Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, for carrying out the nitrogen analyses reported.

A 10- to 15-mg. sample of each androgen, dissolved in 1–2 cc. of ethanol, was allowed to react with a 10 per cent excess of reagent (prepared by adding 2 or 3 drops of concentrated hydrochloric acid to the calculated amount of the free base dissolved in a minimum of hot alcohol), and the mixture boiled for about 2 minutes. Frequently the hydrazone precipitated immediately from the hot solution, but if it did not, water was added to the point of cloudiness. On cooling, precipitation occurred. The precipitate was filtered off, washed with water to remove hydrochloric acid, and dried *in vacuo* over phosphorus pentoxide. After solution in benzene, it was adsorbed on activated alumina (Aluminum Ore Company, Grade F 20, minus 80 mesh), and the chromatogram developed with 10–15 per cent chloroform in benzene. On this adsorbent the bands formed may be brown, orange, or yellow, depending upon the individual compound and to some extent on the developing mixture. Following development, either the column was extruded and cut or, if extrusion proved difficult, the colored zones were dug out with a spatula. The hydrazones of the androgens prepared to date are all readily soluble in benzene and chloroform, moderately so in hot alcohol, but only slightly soluble in ligroin.

After elution with chloroform and filtration, the solvent was removed by distillation under reduced pressure and the hydrazone recrystallized from hot aqueous ethanol to constant melting point. Crystallization from benzene-ligroin pairs produced no change in melting point, but the color of the crystals was usually different from that seen when alcohol was employed. Yields of 95–100 per cent of theory are readily obtained.

TABLE 1

Androgen	M.P.*	Crystalline form and color	N found (%)	N calculated (%)
Testosterone	202.5°–203.5°	Red needles	11.62	11.96
Testosterone propionate	209.9°–210.5°	" "	10.67	10.68
Methyl testosterone	221.5°–223.5°	Orange "	11.41	11.86
Androsterone	232.5°–234°	Yellow "	11.68	11.91
Dehydroisoandrosterone	241°–242°	Yellow micro needles in thick mat	—	—

* Melting points were determined with an aluminum block apparatus calibrated by means of the U.S.P. melting-point reference standards, but are not otherwise corrected.

Table 1 lists the data for the androgen hydrazones prepared to date.

When a mixture of the hydrazones of testosterone and testosterone propionate was subjected to chromatographic adsorption, as described above, the constituents were readily separated and recovered in yields of 97 per cent and 91 per cent respectively, the fractions being identified by melting-point determination after recrystallization. The derivative of testosterone was adsorbed at the top of the column and that of the propionate below.

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Book Reviews

Veterinary bacteriology. (3rd ed.) Ival Arthur Merchant. Ames, Ia: Iowa State College Press, 1946. Pp. viii + 683. (Illustrated.) $7.00.

The third edition of Merchant's *Veterinary bacteriology* will be welcomed by teachers, students, and practitioners. Practically all the bacteria which cause diseases in domestic animals are discussed. In addition, several which affect only man, such as *Eberthella typhosa*, are included. The text is well written, thoroughly comprehensive, and most valuable for instructional and reference purposes. It should be on the shelf of all practitioners and in the libraries of veterinary students. The illustrations are well chosen and typography is good.

Sections on the general biology of microorganisms, infection, resistance, and immunity, and discussions on pathogenic yeast, molds, and viruses, with chapters on the spirochetes, rickettsiae, bacteriophage, and the pleuropneumonia group, are welcome additions, as is the chapter on antibiotics. Reference to *Proteus ammoniae*, *Hemophilus bovis*, and *Clostridium sordellii* is a valuable addition.

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Rehabilitation through better nutrition. Tom D. Spies. Philadelphia-London: W. B. Saunders, 1947. Pp. iv + 94. (Illustrated.) $4.00.

Experiences with folic acid. Tom D. Spies. Chicago: Year Book Publishers, 1947. Pp. 110. (Illustrated.) $3.75.

Both of these small books are essentially reports of clinical researches in nutrition conducted at the Hillman Hospital, Birmingham, Alabama. The monograph on folic acid is an excellent résumé of studies of this important element of the vitamin B complex and the role which folic acid plays in hematopoiesis. Evidence is presented supporting the contention that folic acid is as effective as is liver extract in stimulating blood regeneration in patients with pernicious anemia, nutritional macrocytic anemia, sprue, and pellagra. However, folic acid does not protect the patient from the central and peripheral changes in the nervous system so commonly present in pernicious anemia. Furthermore, large amounts are necessary to produce as satisfactory a hematopoietic response as that obtained with liver extracts, which contain but minute quantities of folic acid. It is highly probable that other elements, as yet undiscovered, are involved in primary pernicious anemia. The volume contains a carefully selected bibliography of some 80 titles.

Rehabilitation through better nutrition does not live up to its overly ambitious title. This 94-page monograph is essentially a report of the studies on the many grossly undernourished patients seen in the nutrition clinic: florid pellagra, sprue, scurvy, and deficiency anemias respond brilliantly to adequate nutritional therapy. The limitations of vitamin and mineral supplemental feeding are clearly stated; when prolonged deficiency has existed and the reserves have been depleted for some time, certain irreversible effects result which are not amenable to vitamin or mineral therapy. A thorough discussion of the variability in requirements points out the invalidity of the assumption that the minimum food requirements are constant. Requirements are affected by race, age, environment, health, work, and the like.

Enthusiasm is as necessary for scientific research and the advance of knowledge as are the vitamins to normal growth. But when enthusiasm leads to such asymmetry of thinking that perspective is lost, it ceases to be wholly desirable. The glitter of the brilliant discoveries concerning the vitamins, trace minerals, hormones, enzymes, and the like has blinded too many students of nutritional problems. The recent literature on nutrition is filled with the erroneous assumption that malnutrition means only deficiency in nutrition. Malnutrition is bad nutrition and includes the effects of excesses as well. Obesity is just as much a nutritional disease as pellagra or rickets or scurvy. As a menace to national health and therefore a problem of social medicine, obesity is more significant than undernutrition, despite the asymmetric emphasis of gross deficiency states in the South. We should not ignore the fact that 28 per cent of the population of the United States are 10 per cent or more *over* their optimum weight, whereas only 12.8 per cent are 10 per cent or more *under* their mean normal weight. However, there is no mention whatever of rehabilitation of the obese in Dr. Spies's monograph. Nor is there mention of the importance of water as a nutritional necessity. If the title were "Therapy of Gross Nutritional Deficiencies," the reviewer would have nothing but praise for this scholarly, scientific report. As it is, one fears that certain uncritical readers will feel that the rules formulated therein are the answer to all of mankind's ills.

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Animal nutrition. (2nd ed.) Leonard A. Maynard. New York-London: McGraw-Hill, 1947. Pp. xviii + 494. (Illustrated.) $5.00.

The second edition of this text presents the chemistry and physiology of nutrition with application to the feeding of farm animals in much the same sequence and style as the first.

During the 9 years since the first edition of this book appeared, significant advances have been made. Of particular importance have been the advances in the field of the vitamins, enzymes, amino acids, and minerals. The author, in bringing the work up to date, has extensively revised many sections of the text and made deletions of less important material, thereby keeping the book close to its original size.

The book is well written in an interesting, readable, and understandable style. The literature citations and reference lists are exceptionally well chosen and should prove particularly helpful to the student.

As before, this book fills a niche in the literature for instructional purposes where suitable texts are not numerous.

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